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Efficacy of Niraparib Therapy in Patients With Newly Diagnosed Advanced Ovarian Cancer by *BRCA* and Homologous Recombination Status: PRIMA/ENGOT-OV26/GOG-3012 Study

Bradley J. Monk,[1] Sileny Han,[2] Bhavana Pothuri,[3] Mansoor R. Mirza,[4] Robert Burger,[5] Florian Heitz,[6] Linda Van Le,[7] Lydia Gaba,[8] David Bender,[9] Eva Guerra,[10] Noelle Cloven,[11] Jacob Korach,[12] Dana Chase,[1] Cristina Churruca,[13] Paul DiSilvestro,[14] Philippe Follana,[15] Jean-François Baurain,[16] Kris Jardon,[17] Carmela Pisano,[18] Paul Hoskins,[19] Sakari Hietanen,[20] Izabela Malinowska,[21] Yong Li,[21] Divya Gupta,[21] Antonio Gonzalez-Martin[22]

[1]Arizona Oncology (US Oncology Network), University of Arizona College of Medicine, Creighton University School of Medicine, Phoenix, AZ, USA; [2]Department of Obstetrics and Gynecology, University Hospitals Leuven, Leuven, Belgium; [3]Gynecologic Oncology Group (GOG) and the Department of Obstetrics/Gynecology, Perlmutter Cancer Center, NYU Langone Health, New York, NY, USA; [4]The Nordic Society of Gynaecological Oncology (NSGO) & Rigshospitalet–Copenhagen University Hospital, Copenhagen, Denmark; [5]University of Pennsylvania, Philadelphia, PA, USA; [6]Department for Gynecology and Gynecologic Oncology, Kliniken Essen-Mitte, Essen, Germany; [7]Department of Ob/Gyn, Division of Gynecologic Oncology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [8]Medical Oncology Department, Hospital Clinic de Barcelona, Barcelona, Spain; [9]Department of Obstetrics and Gynecology, University of Iowa, Iowa City, IA, USA; [10]Medical Oncology Department, Breast and Gynecological Cancer Unit, Hospital Ramon y Cajal, Madrid, Spain; [11]Texas Oncology, Fort Worth, TX, USA; [12]Department of Oncology, The Chaim Sheba Medical Center, Sackler Medical School Tel Aviv University, Ramat Gan, Israel; [13]Hospital Universitario Donostia, Gipuzkoa, Spain; [14]Department of Obstetrics and Gynecology, Women and Infants Hospital/Alpert School of Medicine at Brown University, Providence, RI, USA; [15]GINECO and Centre Antoine Lacassagne, Nice, France; [16]Université Catholique de Louvain and Cliniques Universitaires Saint-Luc, Brussels, Belgium; [17]Department of Obstetrics and Gynecology, McGill University, Montreal, QC, Canada; [18]Department of Urology and Gynecology, Istituto Nazionale Tumori IRCCS Fondazione G. Pascale, Naples, Italy; [19]British Columbia Cancer Agency, Vancouver Centre, Medical Oncology, Vancouver, BC, Canada; [20]Department of Gynecology, Turku University Hospital, Turku, Finland; [21]GlaxoSmithKline, Waltham, MA, USA; [22]Grupo Español de Investigación en Cáncer de Ovario (GEICO) and Medical Oncology Department, Clínica Universidad de Navarra, Madrid, Spain

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PARPi: From Recurrent OC to 1L Setting

- Niraparib was the first PARPi approved as maintenance for recurrent OC regardless of biomarker status, on the basis of the NOVA trial
  - g*BRCA*mut: hazard ratio 0.27 (95% CI 0.17–0.41, P<0.001)
  - Non-g*BRCA*mut: hazard ratio 0.45 (95% CI 0.34–0.61, P<0.001)[1]
- On the basis of QUADRA trial results, niraparib is approved for advanced OC treated with ≥3 prior lines of chemotherapy and for cancer that is HRd, defined by either a deleterious or suspected deleterious *BRCA* mutation or genomic instability and platinum sensitivity
  - Platinum-sensitive *BRCA*mut ORR, 39%; platinum-sensitive HRd ORR, 26%; duration of response, 9.4 months[2]
- In the PRIMA trial, niraparib provided a clinically significant improvement in PFS in advanced OC after response to 1L platinum-based chemotherapy in the overall population (ITT)[3]
  - HRd population: hazard ratio 0.43 (95% CI 0.31–0.59, P<0.001)
  - Overall population: hazard ratio 0.62 (95% CI 0.50–0.76, P<0.001)

1. Mirza MR, *N Engl J Med* 2016;375:2154–2164; 2. Moore KN, *Lancet Oncol* 2019;20:636–648; 3. González-Martín A, *N Engl J Med* 2019;381:2391–2402.
1L, first-line; CI, confidence interval; g*BRCA*mut, germline *BRCA* mutant; HRd, homologous recombination deficient; ITT, intention-to-treat; mut, mutant; OC, ovarian cancer; ORR, objective response rate; PARPi, poly (ADP-ribose) polymerase inhibitor; PFS, progression-free survival.

PRIMA Designed to Address the Unmet Need in 1L Treatment for Advanced OC

Hypothesis: PRIMA/ENGOT-OV26/GOG-3012 tested the efficacy and safety of niraparib after response to platinum-based chemotherapy in newly diagnosed advanced OC, including patients at highest risk of relapse (ClinicalTrials.gov: NCT02655016)

Key inclusion criteria
• High-grade serous or endometrioid adenocarcinoma on histology • Stage III: PDS with visible residual disease after surgery or NACT or inoperable • Stage IV: PDS regardless of residual disease, NACT, or inoperability • CR or PR after platinum-based 1L treatment • Tissue for homologous recombination testing was required at screening (Myriad myChoice®)

Key exclusion criteria
• Patients with stage III disease who have had complete cytoreduction (ie, no visible residual disease) after PDS

1L, first-line; CR, complete response; NACT, neoadjuvant chemotherapy; OC, ovarian cancer; PDS, primary debulking surgery; PR, partial response.

PRIMA Trial Design

Patients with newly diagnosed OC at high risk for recurrence after response to 1L platinum-based chemotherapy

2:1 Randomization

Niraparib | **Placebo**

Stratification factors

- NACT administered: yes or no
- Best response to 1L platinum therapy: CR or PR
- Tissue homologous recombination test status: HRd or HRp/HRnd
  - Determined by Myriad myChoice® next-generation sequencing test

Protocol amendment, November 2017

One-third of patients enrolled received the following starting dose:

- Body weight ≥77 kg and platelet count ≥150,000/μL: 300 mg QD
- Body weight <77 kg and/or platelet count <150,000/μL: 200 mg QD

Endpoint assessment

Primary endpoint: PFS by BICR

Key secondary endpoint: OS

Secondary endpoints: PFS2, TFST, PROs, safety

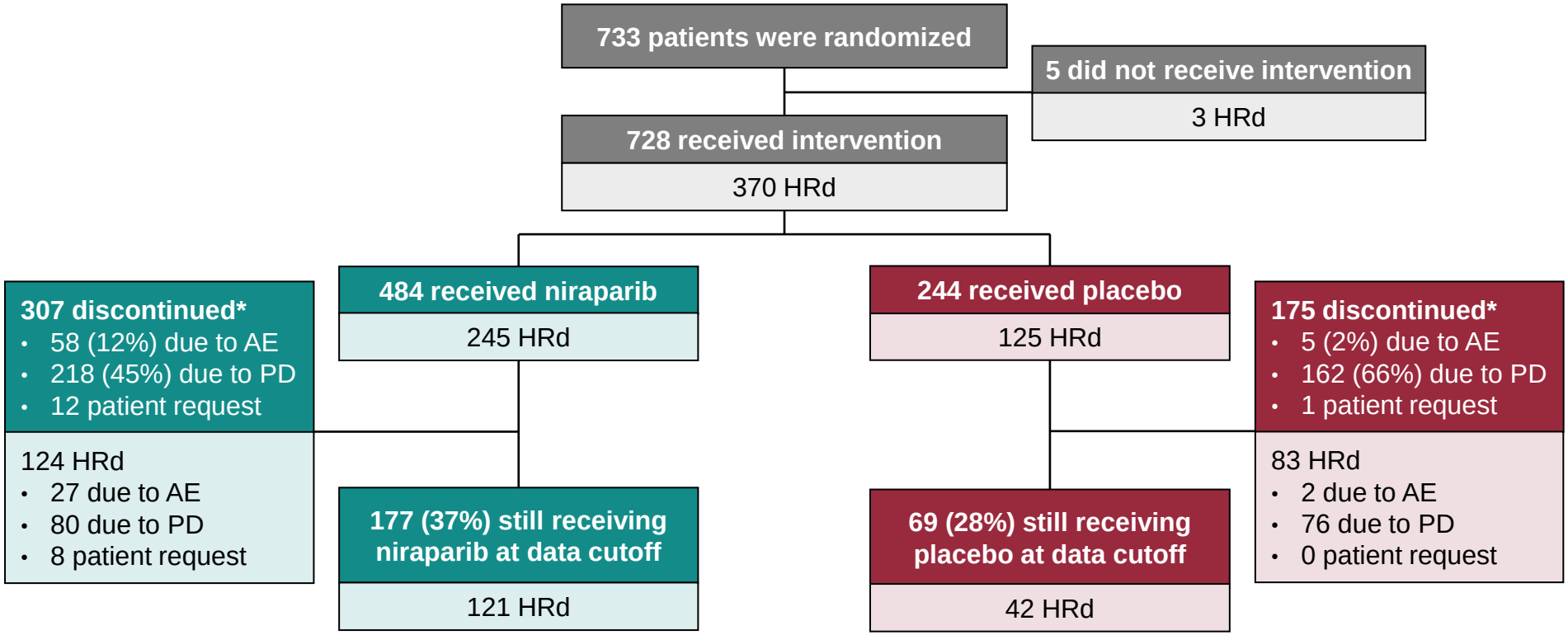
Hierarchical PFS testing

- **Patients with HRd tumors**, followed by the **ITT/overall population**
- Statistical assumption: a hazard ratio benefit in PFS of:
  - 0.5 in patients with HRd tumors
  - 0.65 in the overall population
- >90% statistical power and one-sided type I error of 0.025

https://myriadmychoice.com/portfolio/ovarian-cancer/mychoice-hrd-ovarian-cancer/#result.

1L, first-line; BICR, blinded independent central review; CR, complete response; HRd, homologous recombination deficient; ITT, intention-to-treat; NACT, neoadjuvant chemotherapy; OC, ovarian cancer; OS, overall survival; PFS, progression-free survival; PFS2, progression-free survival 2; PR, partial response; PRO, patient-reported outcome; QD, once daily; TFST, time to first subsequent therapy.

PRIMA Enrollment and Outcomes



- Median follow-up of 13.8 months

Data cutoff: May 17, 2019.
*19 patients (8 HRd) and 7 patients (5 HRd) discontinued for other reasons in the niraparib and placebo arms, respectively.
AE, adverse event; HRd, homologous recombination deficient; PD, progression of disease.

PRIMA Baseline Patient Characteristics and Demographics

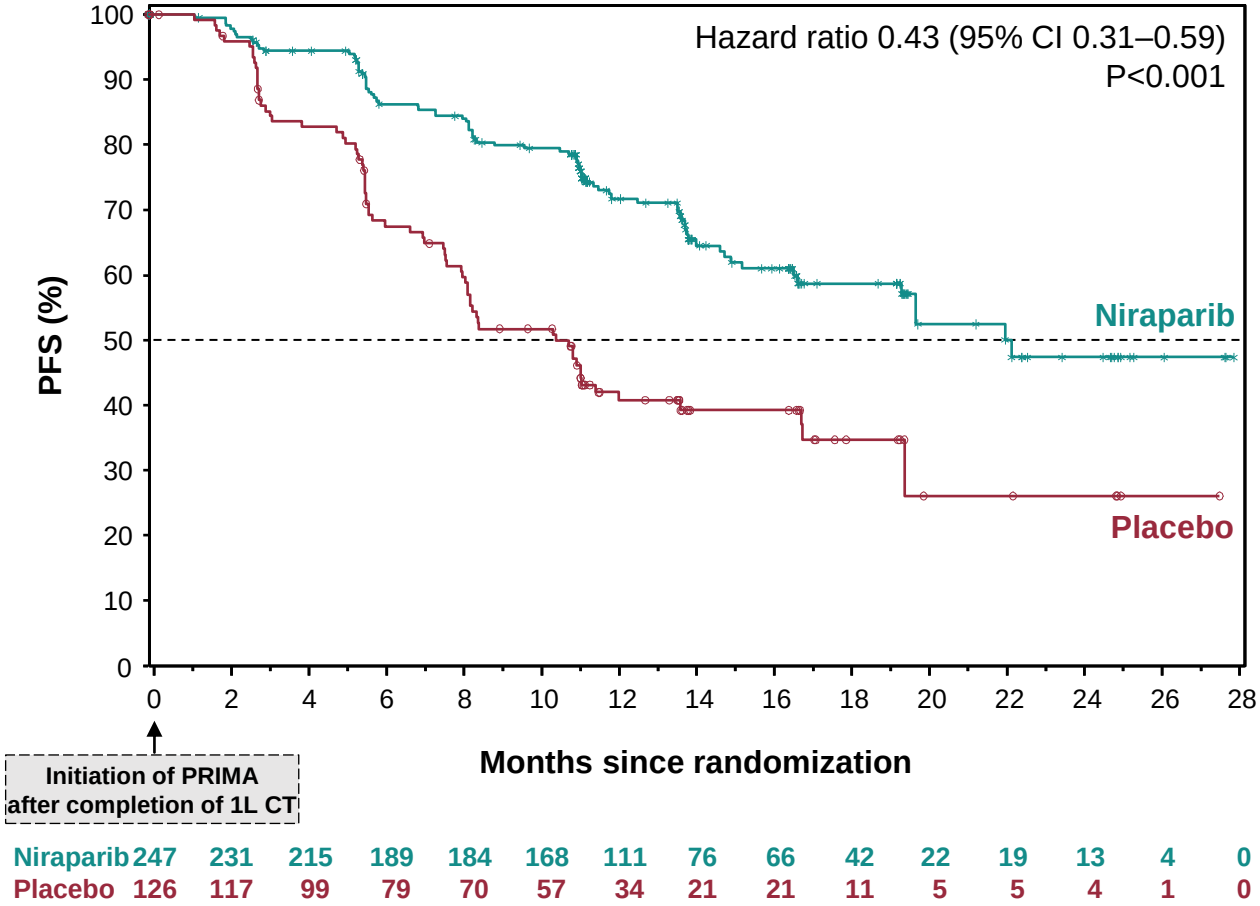
Characteristic	Niraparib (n=487)	Placebo (n=246)	Overall (N=733)
Age, median (range), years	62 (32–85)	62 (33–88)	62 (32–88)
Weight, median, kg	66	66	66
Stage at initial diagnosis, n (%)			
III	318 (65)	158 (64)	476 (65)
IV	169 (35)	88 (36)	257 (35)
Prior NACT, n (%)			
Yes	322 (66)	167 (68)	489 (67)
No	165 (34)	79 (32)	244 (33)
Best response to 1L platinum-based CT, n (%)			
CR	337 (69)	172 (70)	509 (69)
PR	150 (31)	74 (30)	224 (31)
Residual disease after PDS or IDS,* n (%)			
No visible disease	224 (46)	117 (48)	341 (47)
Visible disease	220 (45)	112 (46)	332 (45)
No surgery	13 (3)	3 (1)	16 (2)
Homologous recombination test status, n (%)			
HRd	247 (51)	126 (51)	373 (51)
*BRCA*mut	152 (31)	71 (29)	223 (30)
*BRCA*wt	95 (20)	55 (22)	150 (20)
HRp	169 (35)	80 (33)	249 (34)
HRnd	71 (15)	40 (16)	111 (15)

Overall:

- 35% of patients had stage IV cancer
- 67% received NACT
- 31% achieved a PR to 1L platinum-based CT
- 51% had HRd tumors
- 30% had *BRCA*mut tumors
- 34% had HRp tumors

*44 patients had missing data (30 niraparib, 14 placebo).
1L, first-line; CR, complete response; CT, chemotherapy; HRd, homologous recombination deficient; HRnd, homologous recombination not determined; HRp, homologous recombination proficient; IDS, interval debulking surgery; mut, mutant; NACT, neoadjuvant chemotherapy; PDS, primary debulking surgery; PR, partial response; wt, wild-type.

PRIMA Primary Endpoint: PFS Benefit in the HRd Population by BICR

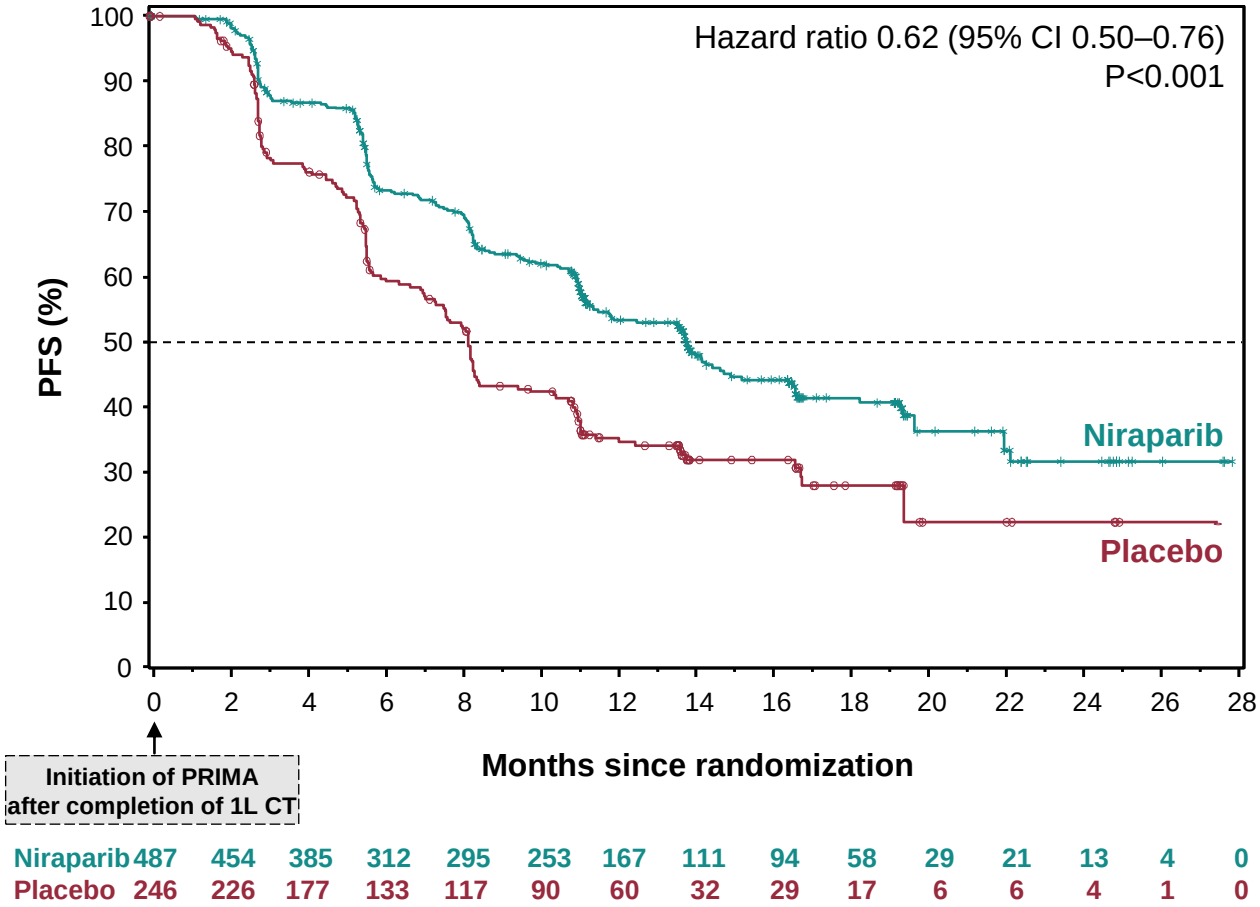


57% reduction in hazard of relapse or death

	Niraparib (n=247)	Placebo (n=126)
Median PFS		
Months (95% CI)	21.9 (19.3–NE)	10.4 (8.1–12.1)
Patients without PD or death, %		
6 months	86	68
12 months	72	42
18 months	59	35

Sensitivity analysis of PFS by the investigator was similar to and supported the BICR analysis.
1L, first-line; BICR, blinded independent central review; CI, confidence interval; CT, chemotherapy;
HRd, homologous recombination deficient;NE, not estimable; PD, progression of disease; PFS, progression-free survival.

PRIMA Primary Endpoint: PFS Benefit in the ITT/Overall Population by BICR



38% reduction in hazard of relapse or death

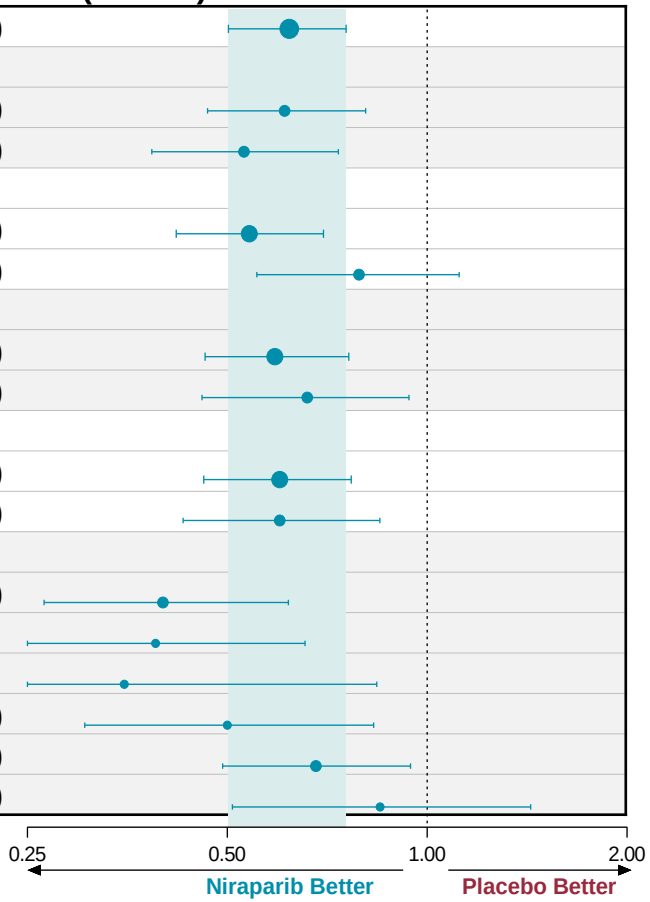
	Niraparib (n=487)	Placebo (n=246)
Median PFS		
Months (95% CI)	**13.8 (11.5–14.9)**	**8.2 (7.3–8.5)**
Patients without PD or death, %		
6 months	**73**	**60**
12 months	**53**	**35**
18 months	**42**	**28**

- High concordance between BICR and investigator-assessed PFS

Discordance in PFS event between investigator assessment and BICR ≈12%.
1L, first-line; BICR, blinded independent central review; CI, confidence interval; CT, chemotherapy; ITT, intention-to-treat; PD, progression of disease; PFS, progression-free survival.

PRIMA Exploratory Analysis: PFS Benefit in Prespecified Subgroups

	Total no. of patients		
	Niraparib	Placebo	Hazard ratio for PFS (95% CI)
Overall	487	246	0.62 (0.50–0.76)
Age group			
<65 years	297	147	0.61 (0.47–0.81)
≥65 years	190	99	0.53 (0.38–0.74)
Stage of disease at initial diagnosis			
III	318	158	0.54 (0.42–0.70)
IV	169	88	0.79 (0.55–1.12)
NACT			
Yes	322	167	0.59 (0.46–0.76)
No	165	79	0.66 (0.46–0.94)
Best response to platinum therapy			
CR	337	172	0.60 (0.46–0.77)
PR	150	74	0.60 (0.43–0.85)
Homologous recombination test status			
HRd–*BRCA*mut	152	71	0.40 (0.27–0.62)
*BRCA1*mut	105	43	0.39 (0.23–0.66)
*BRCA2*mut	47	28	0.35 (0.15–0.84)
HRd–*BRCA*wt	95	55	0.50 (0.31–0.83)
HRp	169	80	0.68 (0.49–0.94)
HRnd	71	40	0.85 (0.51–1.43)

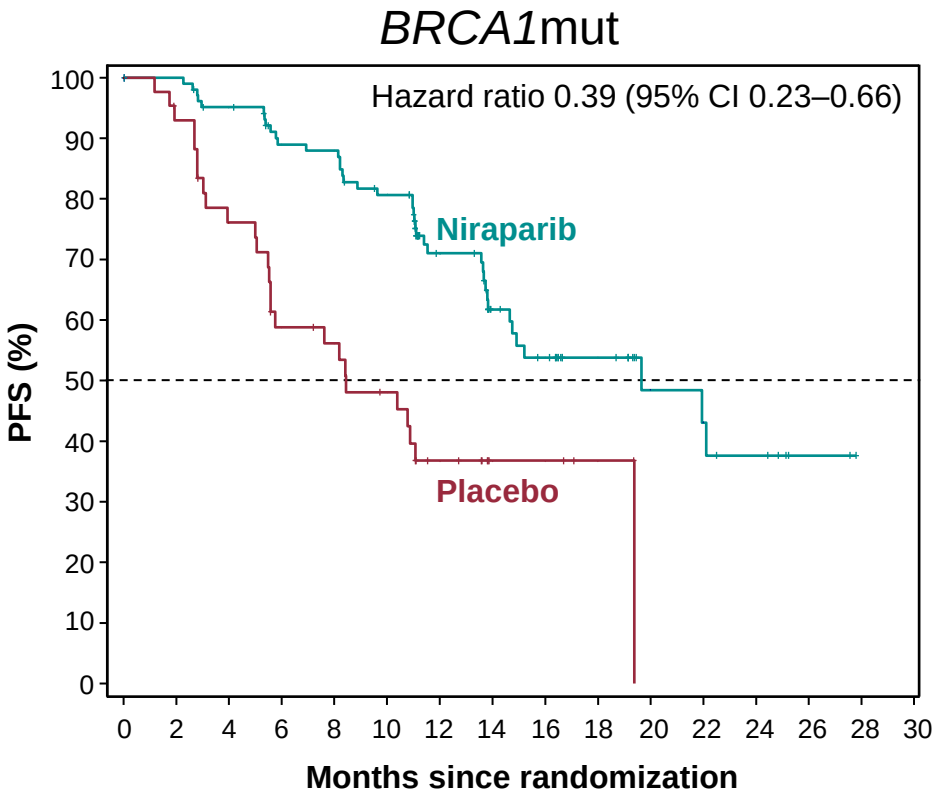


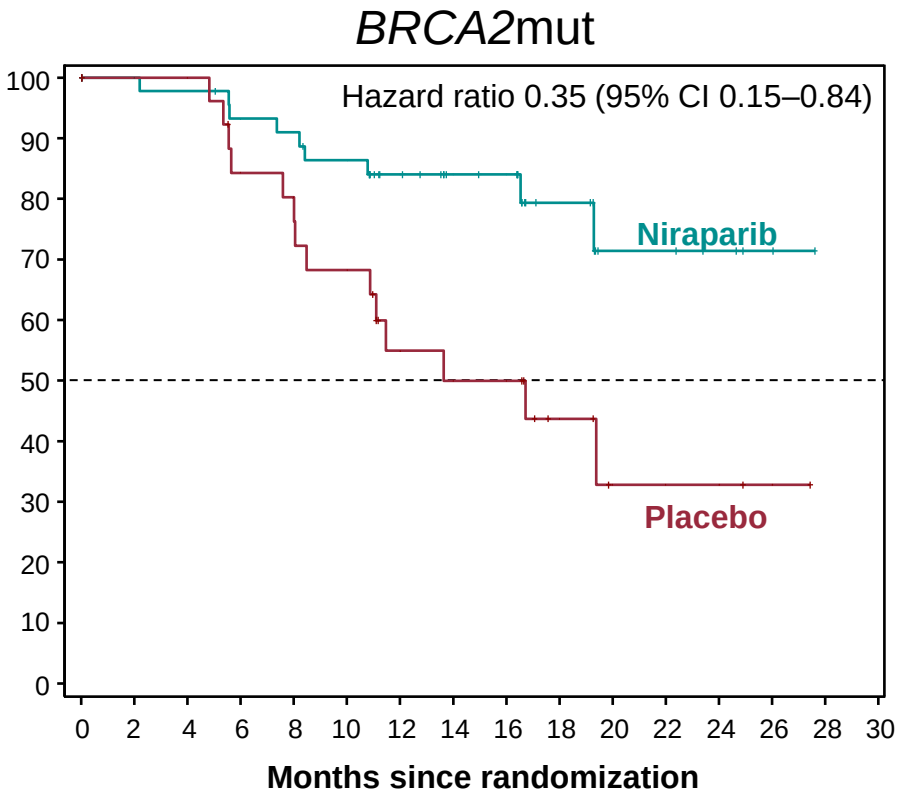
- Hazard ratios are clinically meaningful in all subgroups

CI, confidence interval; CR, complete response; HRd, homologous recombination deficient; HRnd, homologous recombination not determined; HRp, homologous recombination proficient; mut, mutant; NACT, neoadjuvant chemotherapy; PFS, progression-free survival; PR, partial response; wt, wild-type.

PRIMA PFS in *BRCA1*mut and *BRCA2*mut

- Niraparib efficacy was similar in *BRCA1*mut and *BRCA2*mut

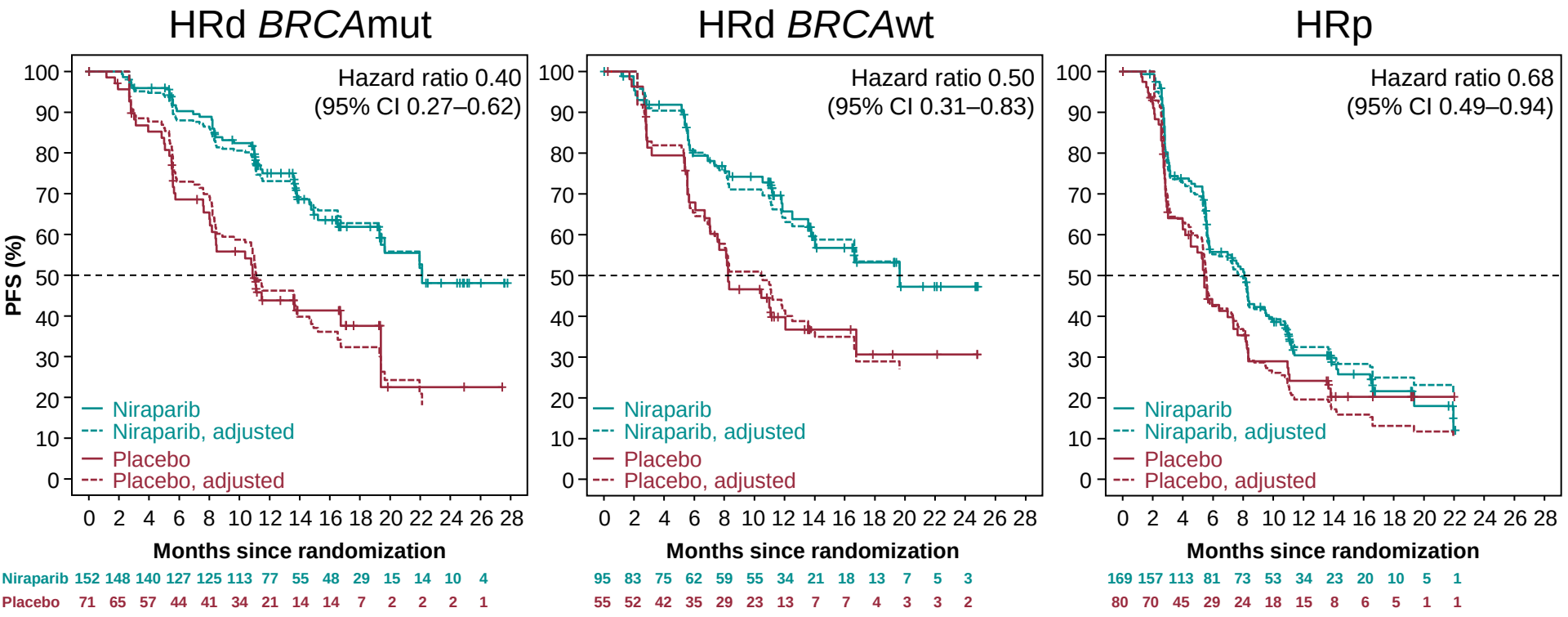




CI, confidence interval; mut, mutant; PFS, progression-free survival.

PRIMA PFS Benefit in HRd and HRp Subgroups by BICR

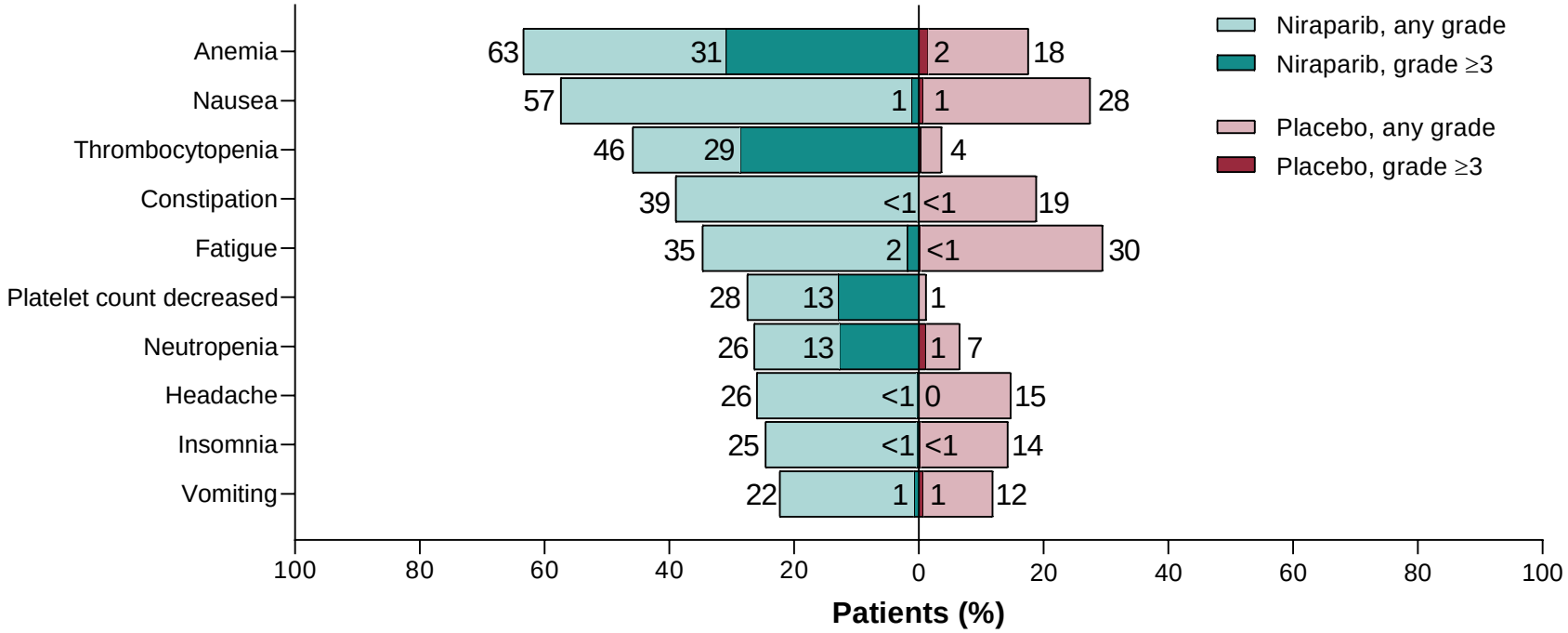
- Niraparib provided clinical benefit in the HRd (*BRCA*mut and *BRCA*wt) and HRp subgroups
- All subgroups were analyzed using the adjusted Cox regression method to account for stratification imbalances



HRd *BRCA*wt population represents all HRd patients who are not *BRCA*mut.
BICR, blinded independent central review; CI, confidence interval; HRd, homologous recombination deficient; HRp, homologous recombination proficient;mut, mutant; PFS, progression-free survival; wt, wild-type.

PRIMA Safety: No New Safety Signals

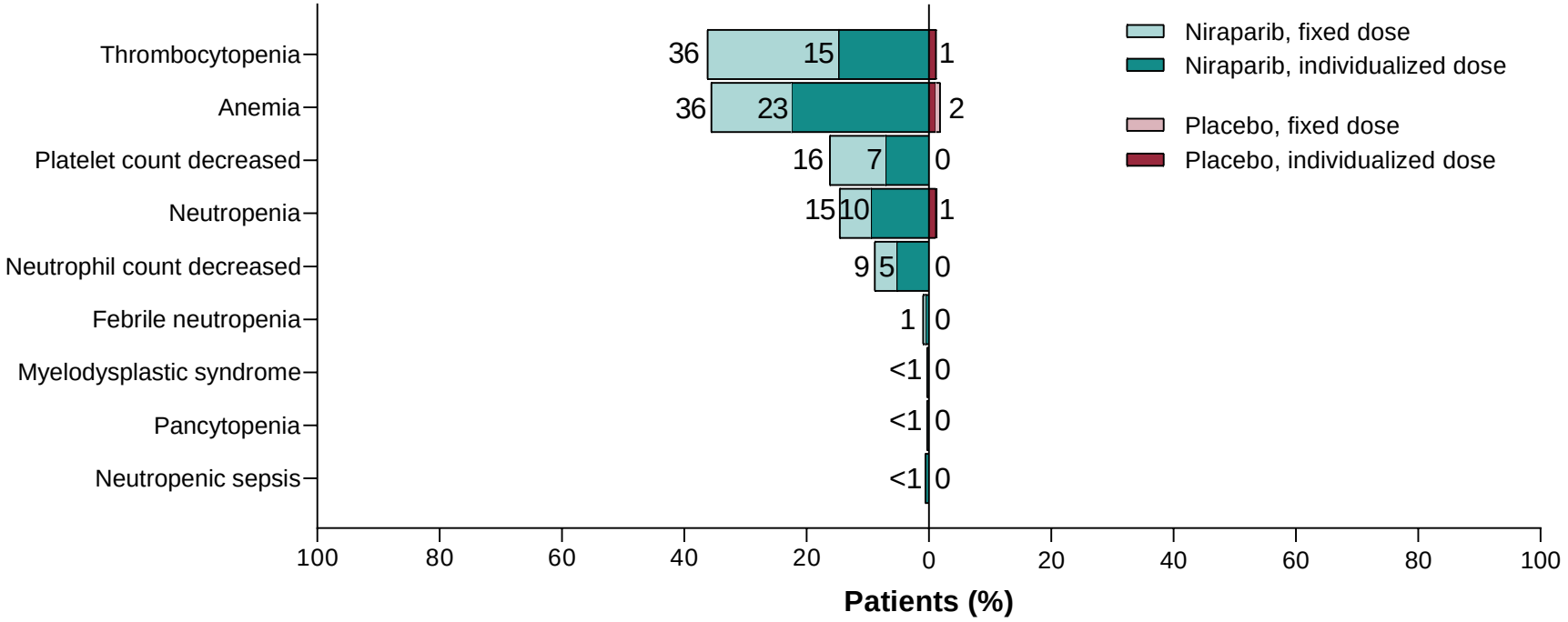
- Dose interruptions were similar to those in the previous niraparib trials
  - Treatment discontinuation due to thrombocytopenia was 4.3%
- No treatment-related deaths
- One patient was diagnosed with MDS after 9 months of niraparib treatment



Thrombocytopenia and low platelet counts are not additive; some patients have both events.
TEAEs >20% incidence in niraparib arm. MedDRA-preferred terms.
MDS, myelodysplastic syndrome; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

PRIMA Grade ≥3 TEAEs: Fixed vs Individualized Dosing

- Incidence of grade ≥3 hematologic TEAEs was lower in patients who received an individualized dose of niraparib compared with patients who received a fixed dose



TEAE, treatment-emergent adverse event.

Conclusions

- Niraparib demonstrated efficacy across biomarker subgroups in NOVA, QUADRA, and PRIMA clinical studies
- In PRIMA, niraparib demonstrated a clinically significant improvement in PFS after response to 1L platinum-based chemotherapy in **ALL** patients
  - PFS HRd: hazard ratio 0.43 (95% CI 0.31–0.59, P<0.001)
    - *BRCA1*mut: hazard ratio 0.39 (95% CI 0.23–0.66)
    - *BRCA2*mut: hazard ratio 0.35 (95% CI 0.15–0.84)
  - PFS overall population: hazard ratio 0.62 (95% CI 0.50–0.76, P<0.001)
  - PFS HRp: hazard ratio 0.68 (95% CI 0.49–0.94)
- Patients with OC at the highest risk of early disease progression (NACT, partial responders to 1L platinum-based chemotherapy) had significant clinical benefit with niraparib
- No new safety signals were observed; individualized dosing regimen reduced high-grade hematologic toxicities
- Niraparib monotherapy could be considered as a new opportunity after 1L platinum-based chemotherapy

1L, first-line; CI, confidence interval; HRd, homologous recombination deficient; HRp, homologous recombination proficient; mut, mutant; NACT, neoadjuvant chemotherapy; OC, ovarian cancer; PFS, progression-free survival.

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